



NYU Medical Center / NYU School of Medicine

Center for Brain Health



Maternal transmission of Alzheimer's disease Prodromal phenotype and the search for genes

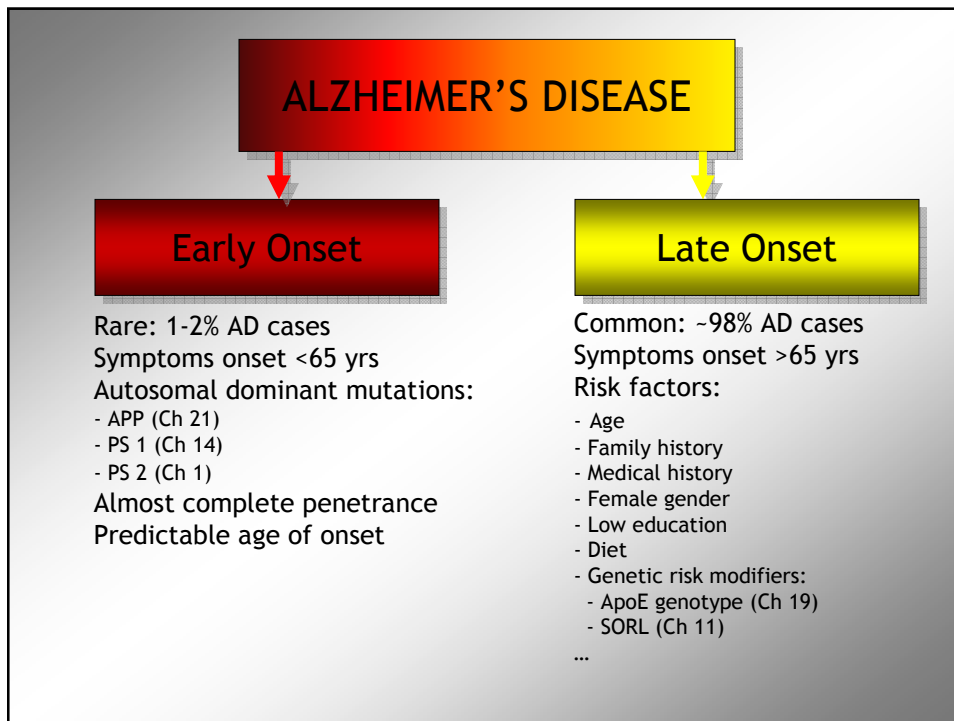
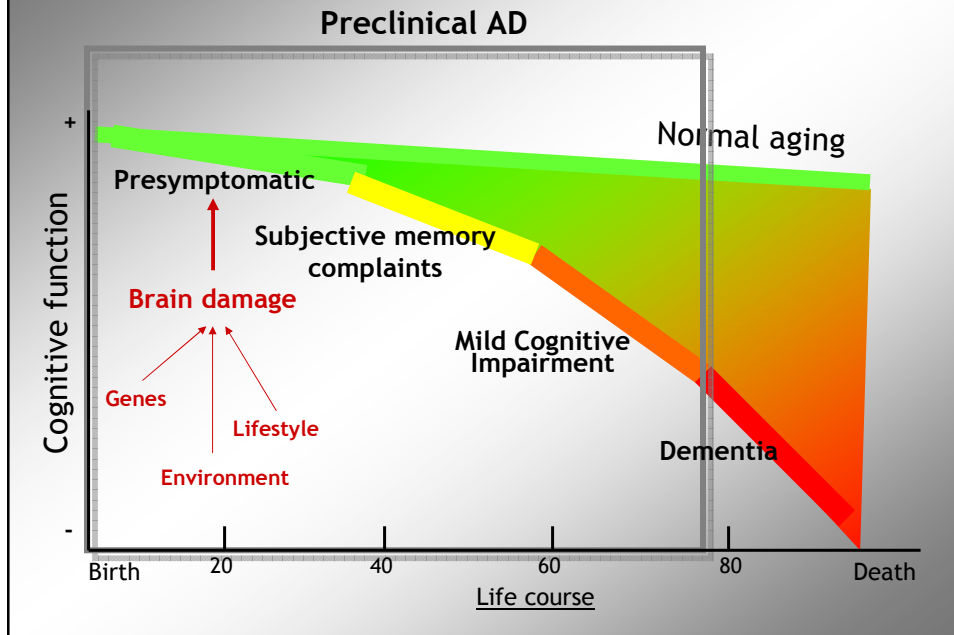
Lisa Mosconi, PhD

Assistant Professor of Psychiatry
New York University School of Medicine

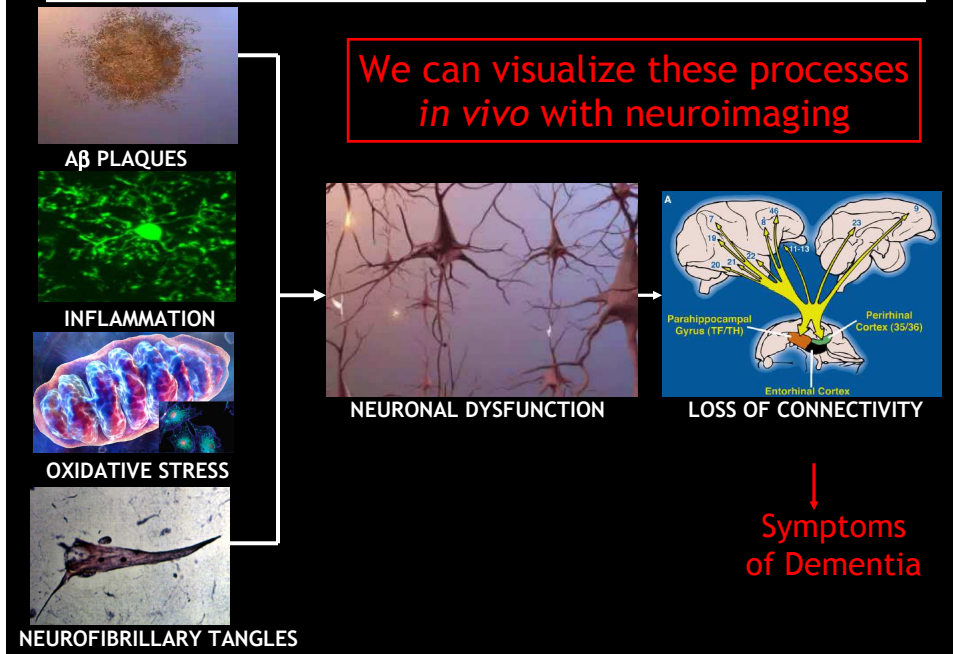
Outline

- Brain imaging has been used to identify biological endophenotypes of incipient AD
- These biomarkers predict decline from normal cognition to dementia with high accuracy (>80%)
- Compare prediction data to findings of similar preclinical brain changes in children of parents affected by late-onset AD

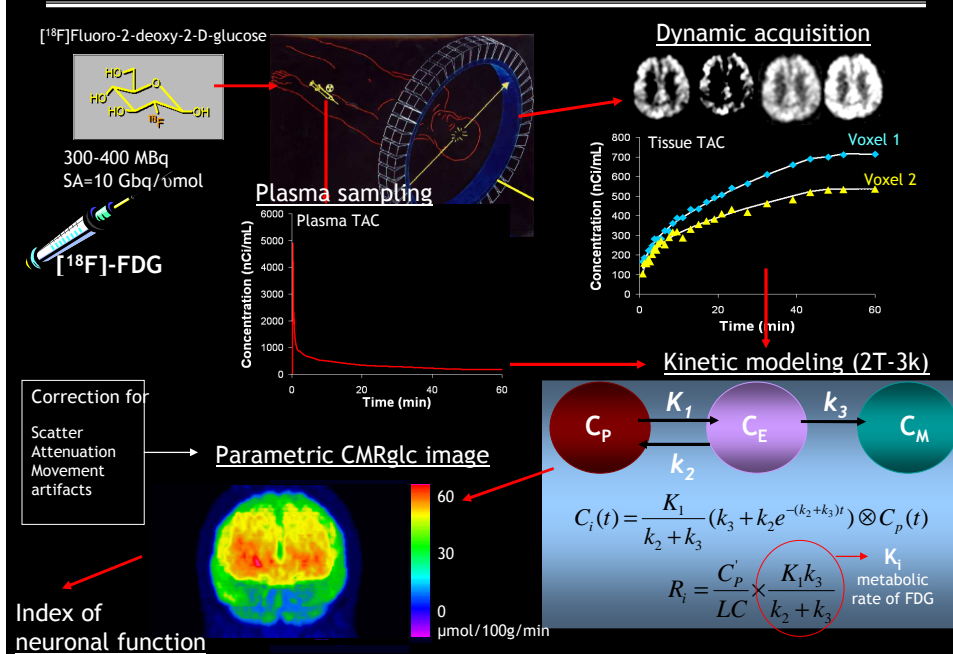
Clinical progression of Alzheimer's disease



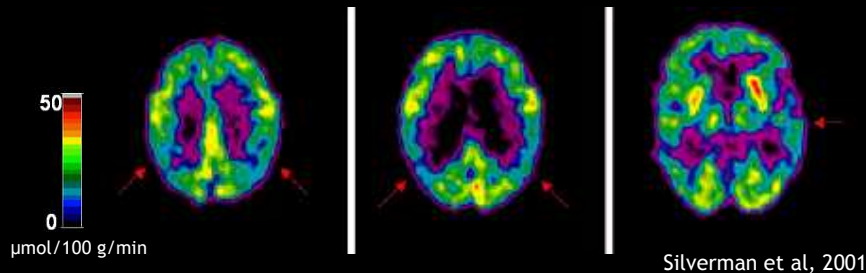
Biological key-players of Alzheimer's



Positron Emission Tomography with FDG



FDG-PET in Alzheimer's disease



The “metabolic signature of AD”:

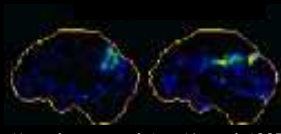
- CMRglc reductions in the parieto-temporal, posterior cingulate, and frontal cortex and medial temporal lobes
- Sparing of occipital, sensori-motor cortex, basal ganglia, cerebellum, pons

FDG-PET findings in preclinical AD

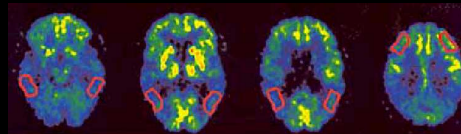
CMRglc reductions on FDG-PET have been observed prior to the onset of dementia in at-risk populations:

- Presymptomatic early-onset familial AD (EOAD)
- Mild Cognitive Impairment (MCI)
- NL with Subjective Memory complaints
- NL elderly (aging)
- NL with an ApoE $\epsilon 4$ allele
- NL with a family history of late-onset AD (LOAD)

MCI show CMRglc reductions prior to decline to LOAD

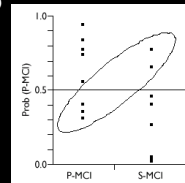


Minoshima et al Ann Neurol 1997



Herholz et al Dem Ger Cog Dis 1999

Reduced CMRglc
 MCI-AD 90% sensitivity
 MCI-MCI 80% specificity

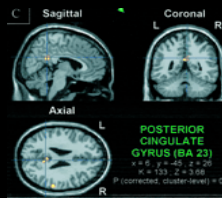


Arnaiz et al Neuroreport 2001

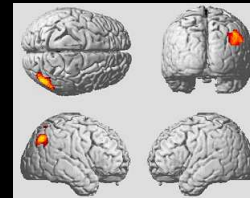


Changes over 1 year

Drzezga et al EJNM 2003



Chetelat et al Neurology 2003



Mosconi et al Neurology 2004

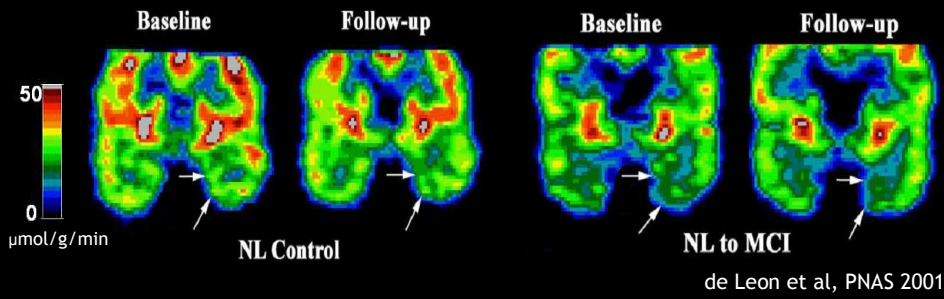
Preclinical Detection Strategies

- Normal elderly
 - Advanced age is the major risk factor for AD
 - NL elderly: 1-3%/yr rate of decline from NL to AD
 - Follow NL elderly until they develop AD

Prediction of decline from NL to MCI

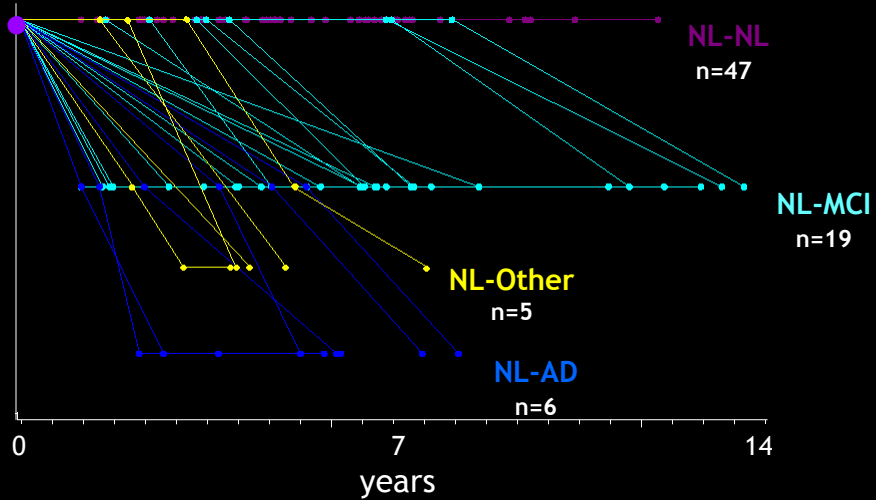
- N=53 NL elderly followed for 3 years
- At follow-up 12 NL declined to MCI

Reduced EC CMRglc
NL-MCI 83% sensitivity
NL-NL 85% specificity

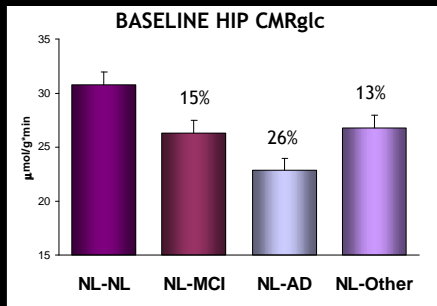


Prediction of Decline from NL to AD

- N=77 NL elderly followed for 6-14 yrs
- Serial clinical, neuropsychological and FDG-PET exams



Prediction of Decline from NL to AD [2]

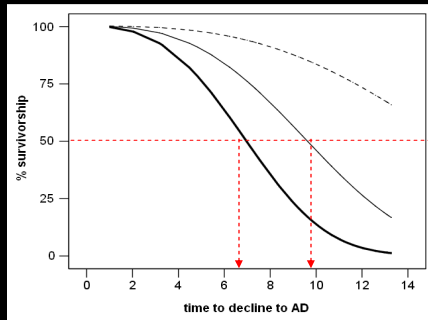


HIP CMRglc prediction accuracy

NL-AD	83%
NL-Other	77%
NL-MCI	71%
NL-NL	81%

Cross-validated accuracy = 79%, P<0.001

- Weibull survival regression model -



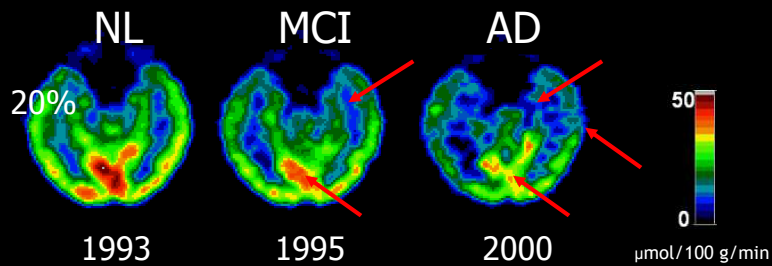
HIP CMRglc

— Hip <24
 - - - Hip 25-29
 · · · · Hip ≥30

Mosconi et al,
 Neurobiol Aging 2007

Before developing AD, predisposed individuals present with:

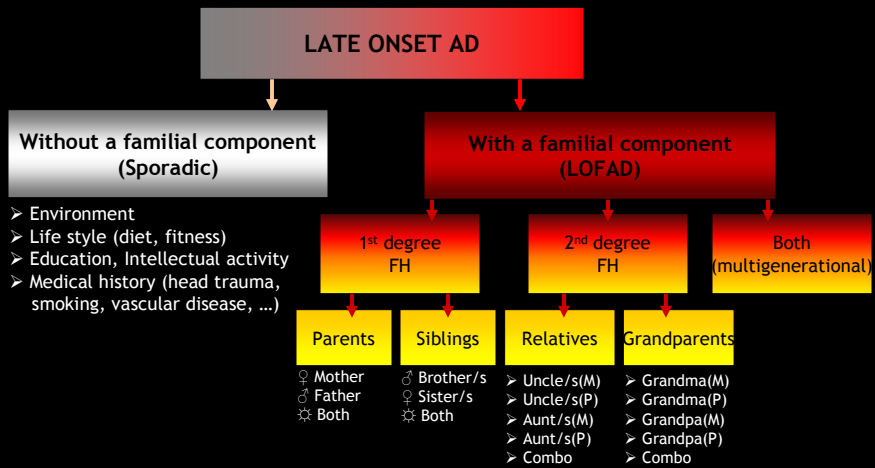
1. Low CMRglc in AD-vulnerable brain regions years prior to the onset of clinical symptoms
2. Progressive CMRglc reductions in AD-vulnerable regions



Mosconi L et al EJNM 2009

NL individuals with a family history of LOAD

While some LOAD cases are sporadic, genetically mediated risk is evident from the familial aggregation of many cases



Mosconi et al, Human Genomics 2009

NL individuals with a family history of LOAD

- NL with LOFAD are at 4-10 times greater risk than NL with negative family history
 - Risk is particularly high when a parent is affected
 - NL with a maternal FH are at higher risk than those with a paternal FH
 - 20-30% of all LOFAD cases are maternally inherited vs <10% paternally inherited
 - NL with LOAD-mothers show a more predictable age at onset, and poorer cognitive performance than NL with LOAD-fathers
- ⇒Epidemiological findings have not been characterized with biomarkers, and LOFAD endophenotypes are unexplored

Barbra Streisand's mother
(singer)

Peter Gallagher's mother
(actor)

Rita Hayworth (actress)

Ronald Reagan & mother
(40th Pres USA)

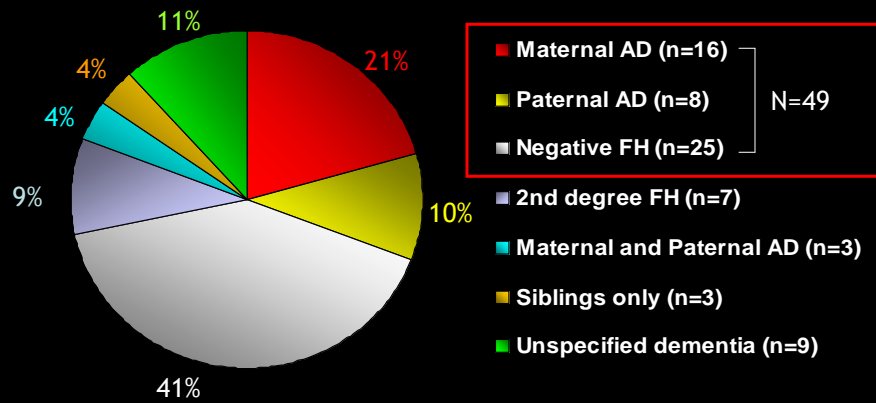
Jim Broadbent's mother
(actor)

Burgess Meredith
(Actor)

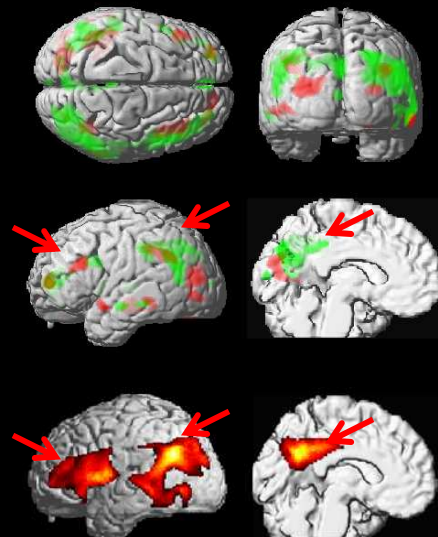
Yasmine Aga Khan's
mother

Our FDG-PET NL database: family history of LOAD

N=78 NL, age 46-85 yrs, edu \geq 12 yrs, 60% F
CDR=0, GDS \leq 2, MMSE \geq 28, Cognitive tests within norms



NL with an AD-affected mother show hypometabolism in the same regions as clinical AD

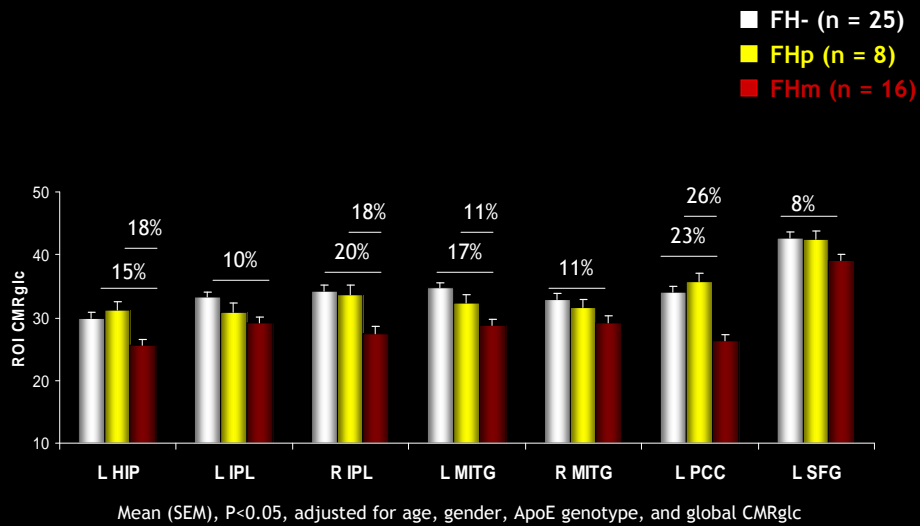


Reduced CMRglc in FHm re: FH-
Reduced CMRglc in FHm re: FHp
P<0.05 FWE corrected

Reduced CMRglc in AD re: CNT

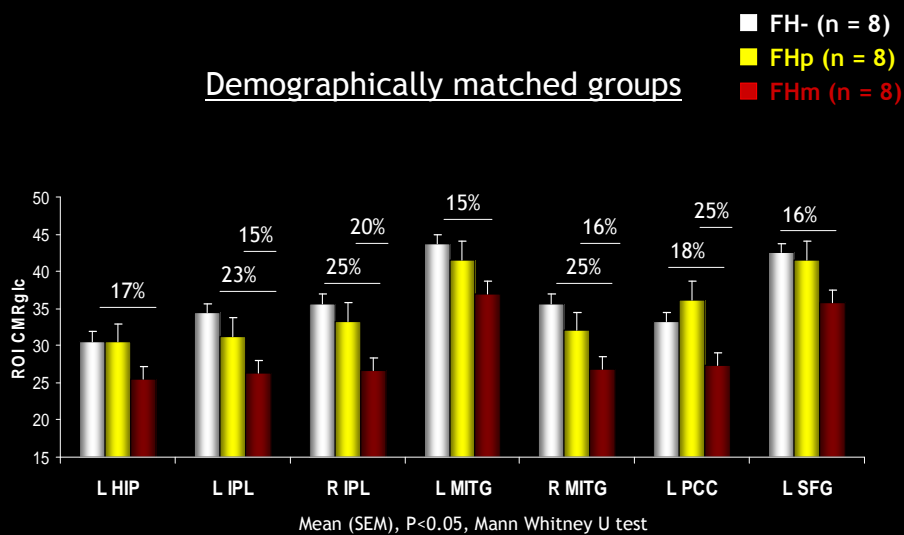
Mosconi et al, PNAS 2007

CMRglc reductions in AD-brain regions in NL FHm



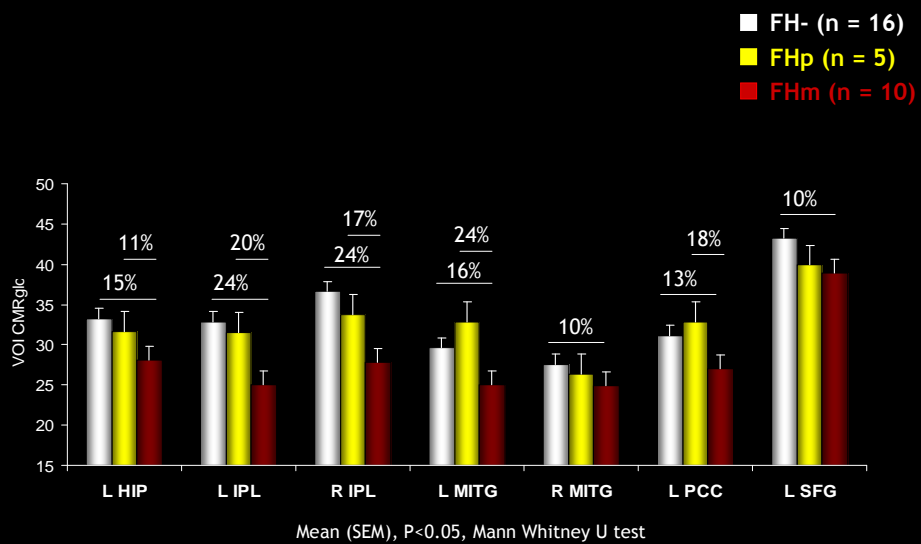
Mosconi et al, PNAS 2007

CMRglc reductions in AD-brain regions in NL FHm [2]



Mosconi et al, PNAS 2007

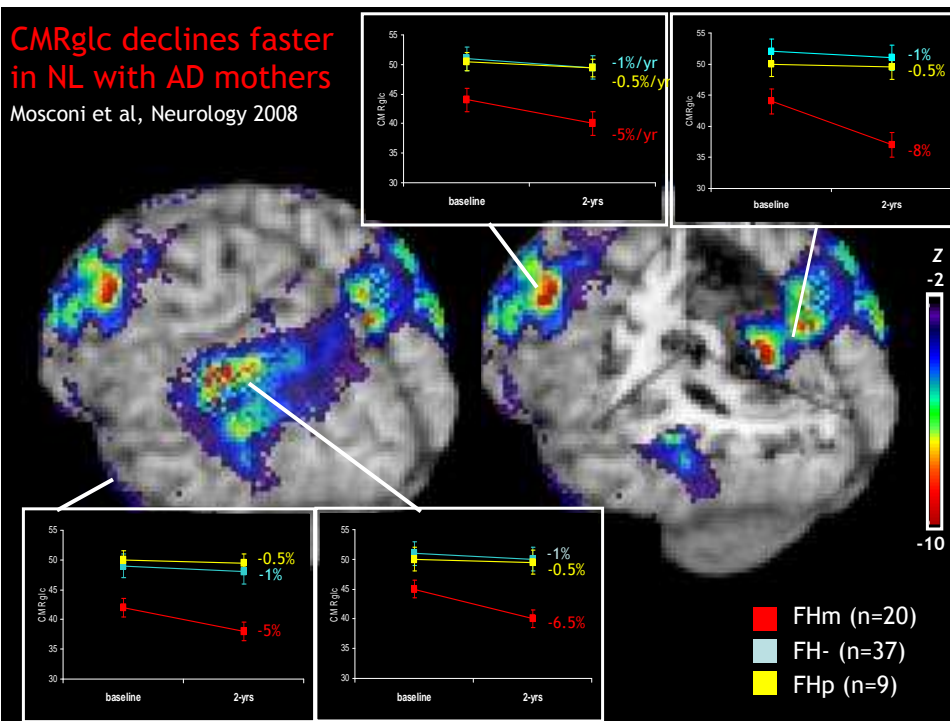
CMRglc reductions in NL FHm ApoE ε4 non-carriers



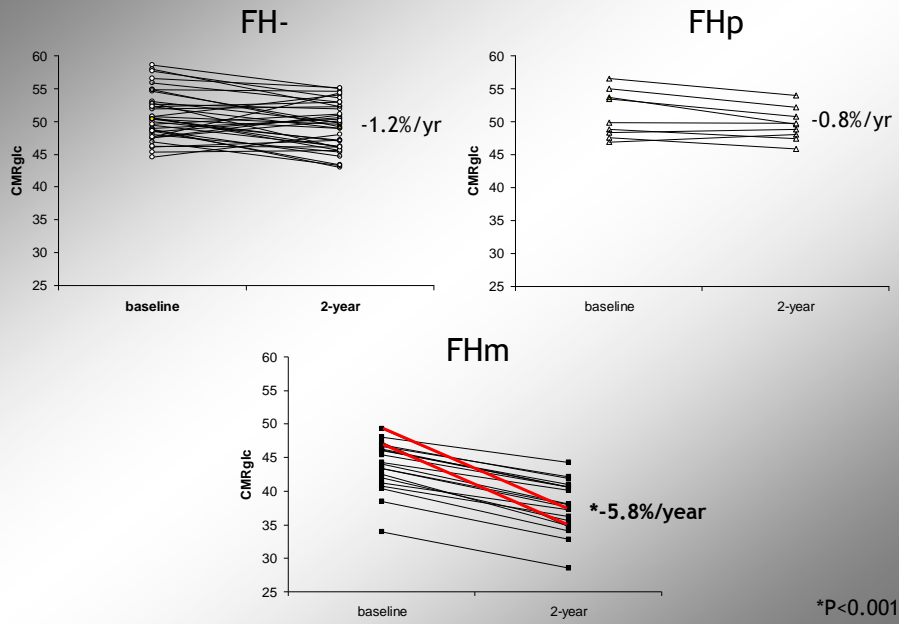
Mosconi et al, PNAS 2007

CMRglc declines faster in NL with AD mothers

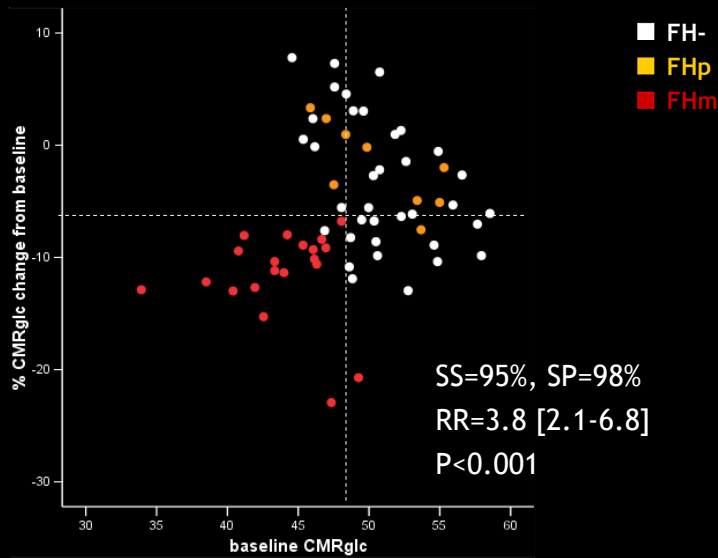
Mosconi et al, Neurology 2008



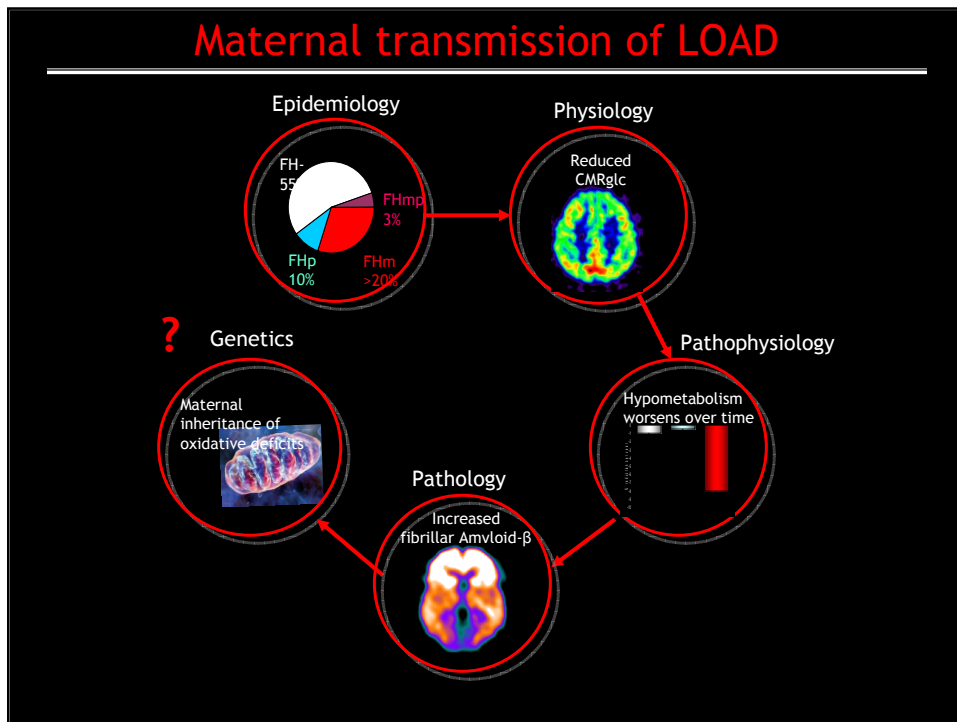
Longitudinal CMRglc reductions in AD-regions



FHm have 4-times greater chances of CMRglc deficits



Maternal transmission of LOAD



The causes of hypometabolism in Fhm are unknown

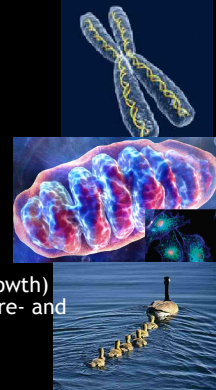
Environment & life-style

- Parents and children share common environments, which could confer risk
- If a parent develops AD late in life, children have greater chance of AD as they also live long (and women live longer than men)



Genetics

- Chromosome X mutations**
 - X-linked inherited diseases transmitted from mother to sons
 - Daughters can become carriers but do not develop disease
- Mitochondrial DNA**
 - 100% maternally inherited in humans
 - Implicated in metabolic dysfunction in AD (cytochrome c oxidase)
- Epigenetic Imprinting**
 - Maternal imprinting is "growth limiting" (inhibition of intra-uterine growth)
 - Metabolic imprinting: epigenetic programming of metabolism during pre- and neo-natal periods
- Genes related to APP metabolism**
- Other ...**



Mosconi et al, Human Genomics 2009

Open questions

- Longitudinal studies are needed to examine the relationship between altered biomarkers, estimated risk and actual clinical decline
- Genetic mechanisms involved in maternal inheritance of oxidative dysmetabolism and amyloidosis in LOAD are not known
- Maternally inherited AD accounts for >20% of all LOAD cases. Usefulness of investigating parent-of-origin effects in LOAD
- NL FHM could be a homogenous at-risk population for clinical trials, to evaluate prevention treatments, and to help direct genetic studies in LOFAD

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Children of post-mortem confirmed AD parents

